ON

THE ACTIONS AND USES

OF

CITRATE OF CAFFEIN AS A DIURETIC.

BY

DAVID J. BRAKENRIDGE, M.D., F.R.C.P.E.,

PHYSICIAN TO THE ROYAL INFIRMARY, AND LECTURER ON CLINICAL MEDICINE, EDINBURGH.

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ON THE ACTIONS AND USES OF CITRATE OF CAFFEIN AS A DIURETIC.

Caffein, the active principle of tea, coffee, cocoa, and guarana, is a very potent substance, the physiological actions of which, in both toxic and therapeutic doses, have received much attention of late years.

On many points, however, the results obtained by different experimenters are very conflicting. I will therefore avoid all discussion of these disputed points at present. The only well-established fact which we have until recently been able to turn to therapeutical account is that caffein is a powerful cerebral stimulant. Hence its chief use, apart from its popular employment in the familiar beverages which contain it, has been as a remedy in nervous headache and opium poisoning.

In January 1879, Dr Lewis Shapter, in a paper in the *Practitioner*, first directed special attention in this country to the citrate of caffein as a diuretic in cases of cardiac dropsy. He, however, acknowledges his indebtedness to Professor Gubler, who had previously shown that the citrate or bromhydrate of caffein, in doses of gr. iv. to gr. viij., given either hypodermically or by the mouth, induces abundant and instantaneous diuresis in such cases.

During the past eighteen months I have prescribed this drug in a large number of cases of cardiac and renal dropsy, both in the wards of the Edinburgh Royal Infirmary and in private practice, and the results which I have obtained have been for the most part confirmatory of the favourable results obtained by these observers, and more recently by Dr Leech.[1]

Some time after commencing the use of the drug, however, I began to fear that it was likely to prove one of those uncertain remedies which, frequently failing us altogether at a critical moment, we learn after a time to discard as untrustworthy, and that I would have to acquiesce in the verdict of Dr Leech, who

[1] *Practitioner*, 1880.

qualifies his otherwise highly favourable opinion with these words: "Most drugs are found to act differently on different individuals, but caffein is specially variable in its effects."

A more careful study, however, of the circumstances under which these failures and variations in the action of the drug have occurred has led me to reverse this unfavourable opinion.

Citrate of caffein has, I believe, a special action, being chiefly a stimulant of the renal glandular epithelium, and very slightly, if at all, a vascular diuretic. It has, therefore, a special and limited place as a diuretic. Acting upon this view of its action, I have never been disappointed in obtaining a marked increase in the flow of urine by its proper employment in suitable cases, and, when necessary, suitably combined with other drugs. But I am afraid it will be impossible to understand the special action claimed for the drug unless we recall to mind the anatomical arrangements in the kidney provided for the separation of the urine, and also the main points bearing on our present subject of what is known regarding the physiology of the process, and especially regarding the part played in it by the renal glandular epithelium.

In this I will purposely, to avoid controversy, confine myself to those physiological data which are accepted as important by most of our leading authorities, although I will draw from these data some warrantable conclusions which appear to me essential to the proper understanding of diuresis and the actions of diuretic drugs. The anatomical arrangements in the kidney for the separation and modification of the urine are threefold, provision being made for—1st, Filtration; 2d, Diffusion; 3d, True Secretion.

First, In each glomerulus, which consists of a cluster of small bloodvessels, the afferent vessel of which is larger than the efferent, and which is enclosed in a capsule, the dilated commencement of a tubulus uriniferus, we have a structure admirably adapted for filtration.

Secondly, In the tubulus uriniferus, which consists of a basement membrane having on the outside applied to it the capillary plexus into which the efferent vessel from the corresponding glomerulus has divided, and on the inside the renal epithelium, provision is made whereby diffusion may readily take place between the urine in the tubule and the blood in the surrounding vessels.

It must be remembered in this connexion that the tubules are further surrounded—according to Ludwig—by lymphatic spaces which freely communicate with one another.

Thirdly, In the glandular epithelium which lines a considerable portion of the tubulus uriniferus,—especially the convoluted cortical portion,—and which in its anatomical characters closely resembles the glandular epithelium of purely secretory organs, we have a structure whose function may *a priori* be expected to be truly secretory.

Physiological experiments and observations have for the most

part tended to confirm the views regarding the functions of the kidneys thus suggested by these anatomical arrangements.

I can only briefly summarize what is at present known on the subject.

First, In the Malpighian body, filtration from the blood in the glomerulus of water containing the soluble constituents of the urine, in proportions definitely related to those in which they pre-exist in the blood, takes place into the capsular dilatation of the tubulus uriniferus.

Other things being equal, the amount of urine thus separated by filtration varies directly with the blood-pressure in the glomerulus. The variations in this blood-pressure—as is well known—depend upon either general or local causes, which I need not detail here.

Second, Diffusion must take place in the tubulus uriniferus; for all the conditions present are such as to favour the passage of water from the urine in the tubule into the veins surrounding it.

a. It is well known that alkaline solutions produce positive osmosis or endosmosis, whereas acid solutions produce negative osmosis or exosmosis. Now the urine in the tubule is acid, whereas the blood in the surrounding venous plexus is alkaline; hence we have here conditions which doubly favour the passage of water from the urine to the blood.

b. Water tends to pass by diffusion from the less concentrated to the more concentrated fluid. In this case the very dilute urine filtered from the glomerulus is much less concentrated than the blood in the venous plexus from which it has just been filtered. Hence, for these reasons, a considerable proportion of water passes from the urine in the tubule back into the blood in the surrounding vessels. The excrementitious urine thus rendered more concentrated passes onwards through the various urinary channels out of the body.

Third, That these purely physical processes do not, as was maintained by Ludwig, entirely explain the secretion of urine, and that the function of the renal epithelium is truly secretory, is *a priori,* from the anatomical standpoint, highly probable. But many facts render this almost certain. For example, disease of the renal epithelial cells seriously interferes with secretion. In birds, uric acid deposits are seen to originate within the cells, the disintegration of which seems necessary before the deposit can become free. After urate of sodium has been injected into the blood the same thing has been observed. Much experimental evidence may be adduced to show that the renal glandular epithelium is a true secreting structure.

It has been demonstrated that when arrest of the natural flow of urine has been caused by section of the spinal cord below the medulla, and consequent lowering of the general blood-pressure, a copious flow of *urine* can be induced by the injection into the blood of such substances as urea, urates, etc

According to C. Ustimowitsch, "this secretion is *unaccompanied by any rise of blood-pressure sufficient to account for the flow on any filtration hypothesis.*" By experiments performed in a similar manner, Heidenhain, who, instead of urea, used indigo-carmine, demonstrated the passage of the pigment through the glandular cells into the channel of the tubule, where it was precipitated in a solid form. This substance, towards which the renal epithelial cells would seem to exert a special secretory selective activity, is well suited for experiment, as it excites no secretion of urine, and thus is not washed away, and can be traced in its progress through the cells.

Henschen[1] and Paulynski[2] have each recently published independent experiments which seem to throw some doubt upon the accuracy of Heidenhain's observations and conclusions, and to indicate that the pigment is separated by filtration, its appearance in the epithelial cells being due to reabsorption. Both observations may be, and probably are, correct; for if, as Heidenhain stated, in his experiments the flow of urine in the kidney was completely arrested by section of the spinal cord, filtration was impossible; whereas if, as is admitted, in Henschen and Paulynski's experiments filtration took place, then the indigo-carmine would certainly be filtered from the glomeruli along with the other soluble constituents of the urine. We have fortunately, however, evidence more conclusive even than that of Heidenhain.

To determine the functions of the two chief divisions of the renal secretory apparatus, Nussbaum experimented on a class of animals in which the blood-supply to the glomeruli is quite distinct from that which supplies the glandular epithelium. In the amphibia the glomeruli receive their blood-supply from the renal artery, whereas the plexus around the tubuli uriniferi is formed by branches which come from a totally different source, viz., one of the two branches into which the femoral vein divides at the top of the thigh. The small efferent vessels from the glomeruli certainly terminate in the so-called "renal portal-plexus," but "actual observation of the kidney of the newt has shown that when the renal artery is tied the blood is shut off from the glomeruli, and not the slightest reflux takes place from the capillary network surrounding the tubules to the glomeruli."[3] The kidney is thus converted into an ordinary secreting gland.

Nussbaum's experiments, performed upon such a kidney, have thrown much light upon the functions of that organ. For our present purpose it is sufficient to state that, having tied the renal artery, and thus completely cut off the blood-supply from the glomeruli, he found that, if urea be injected into the blood, a secretion of *urea* and *urine* takes place. He further injected indigo-

[1] *Akademisk Afhandling för Medicinska Graden*, Stockholm, 1879, p. 166.
[2] Virchow's *Archiv*, Band LXXIX., p. 393.
[3] Foster's *Physiology*, p. 376.

carmine into the blood, and found, as Heidenhain had previously shown, that it is separated by the epithelial cells, where filtration is impossible.

Leaving out of consideration for the present the process of diffusion by which the urine, already separated, merely undergoes concentration, from the foregoing evidence we must conclude—

1*st*, That the glomerulus forms an excellent filtering mechanism, whereby the water and soluble constituents of the urine are, under the influence of blood-pressure, separated from the blood.

2*d*, That the renal glandular epithelium is a true secreting structure, possessing the power of separating from the urine, urea, uric acid, water, and probably other constituents of normal urine.

3*d*, That certain substances, *e.g.*, urea, possess the power of causing increased activity of the epithelial cells.

4*th*, That each of these two structures in the kidney, whereby urine is separated from the blood, possesses the conditions necessary for the separation of the constituents of normal urine.

5*th*, That in the one, the glomerulus, the process is purely physical, viz., by filtration. In the other, the epithelium, it implies a special glandular selective activity.

Hence we may assume that in health, when the blood-pressure and the renal glandular epithelium are both normal, the greater amount of urinary water, holding in solution the soluble constituents of urine in proportions bearing a definite relation to those in which they pre-exist in the blood of the renal artery, is separated from that fluid by filtration in the Malpighian bodies. But a purely physical process, whereby certain soluble substances are separated in purely physical proportions, can never free the blood from each of its impurities in those exact amounts which alone will satisfy the requirements necessary for the maintenance of health. Hence, for the glandular selective function of the renal epithelium is reserved the higher and nicer work of further removing from the blood, in the exact proportions of each necessary for the maintenance of health, those substances which have escaped filtration, and whose retention would be injurious. By this beautiful arrangement the greater but rougher amount of the work is accomplished by the simpler process of filtration, while the lesser but finer and more exact part of the work is done by the higher process of true secretion.

It is evident, then, that these filtering and secreting organs bear a complementary relation to one another, and that the amount of work done by the one must vary inversely with the work done by the other. Thus, on the one hand, the more the urine that is separated by filtration, the less urea, water, etc., will reach the glandular epithelium to be separated by it; and the less the separation of urine in the Malpighian bodies, owing to a fall in the blood-pressure or otherwise, the more urea, urinary water, etc., will reach the glandular renal epithelium and stimulate its secretory activity. Whereas, on the other hand, if the glandular epithelium be either

diseased or exhausted, and less urea, uric acid, etc., be thus separated by it, these, accumulating in the blood, will consequently, in proportionally larger quantities, be filtered from that fluid in the glomeruli. Within the limits of health, the amount of work done by each of these chief factors in the separation of urine must vary constantly and considerably; and when we pass beyond the limits of health the modifications in the balance may become much greater.

From the foregoing facts we may draw the following conclusions:—

1*st*, When the blood-pressure in the glomeruli of the kidney is abnormally lowered, and when thus or from any other cause, such as increased pressure of urine in the capsules, filtration is interfered with, the amount of urine separated in the Malpighian bodies will be proportionally diminished.

2*d*, That, consequently, the solid constituents of the urine will thereby be insufficiently removed from the blood by filtration, and hence will be presented in increased amount to the renal glandular epithelium.

3*d*, That urea, and probably the other constituents of the urine which it is the function of the renal epithelium to separate from the blood, being stimulants of the secretory epithelium, their presence in increased amount will augment the activity of the glandular cells, and cause increased secretion by them, not only of urea, uric acid, etc., but also of water.

4*th*, That thus, in many cases of advanced heart disease, for example, there must take place in time a gradual transference of work from the glomeruli to the secreting epithelial cells, the latter coming, as the blood-pressure is lowered, to take upon them the secretion of more of the urinary water, as well as such solid constituents as urea, uric acid, etc.

5*th*, That this transference of work is not necessarily indicated by the amount or constitution of the urine passed.

For example, take two cases in each of which 20 oz. of urine are passed in the twenty-four hours. In the one the greater amount of the urine may be filtered from the blood in the glomeruli as the result of blood-pressure; in the other it may be secreted by the renal epithelial cells as the result of excessive stimulation from retention in the blood which reaches them of such substances as urea, urates, etc. This fluctuating balance of work between filtration and secretion explains many of the anomalies in the action of diuretic remedies, and for the proper selection and employment of these it seems to us important that we should not only bear it in mind, but determine as far as possible in each case its actual state.

In the foregoing remarks I have assumed that the amount of blood passing through the kidneys has been in all cases the same. It must not, however, be forgotten that the amount of urine secreted by the kidney will, other things being equal, vary directly with the amount of blood which passes through that organ.

Neither blood-pressure in the glomeruli nor secretory activity in

the glandular epithelial cells can separate from the blood more urine than it contains. Hence the amount of urine must always be further conditioned by the amount of blood which circulates through the organ.

It is thus clear that drugs may increase the amount of the urine in some one or more of the following ways:—

1*st*, By increasing the blood-pressure in the glomeruli.

2*d*, By increasing the rapidity of the circulation in, and the amount of blood passing through the kidneys.

3*d*, By stimulating the renal glandular epithelium.

4*th*, By modifying the process of diffusion in the kidneys or in the body elsewhere.

There is no reason to believe that in the large increase of urine caused by citrate of caffein modification of osmosis plays any part, and therefore I will not further discuss it at present, although I have little doubt that some of the saline diuretics, *e.g.*, acetate of potash, act partly at least in this manner. The purely vascular diuretics act by increasing both the blood-pressure in the glomeruli and the amount of blood passed through the kidneys.

Digitalis may be regarded as the type of the class of vascular diuretics. Digitalis increases diuresis by increasing arterial tension and the amount of blood flowing through the kidneys. It "has," says Binz, "no directly stimulating effect on the secretory function of the kidneys," although it may, by thus improving the nutrition of the glandular epithelium, indirectly increase its secretory power and activity. But there is abundant evidence to show that such a purely vascular diuretic as digitalis may, in certain cases, be quite powerless, when given alone, to produce any very marked diuresis.

The fact is quite familiar to every practitioner that digitalis in combination with other drugs will often prove successful where, given alone, it had signally failed. The probability is that many of those drugs which thus increase the action of digitalis act upon the secretory structures of the kidney in some manner quite different from digitalis, either by stimulating the glandular epithelium or by modifying the osmotic processes in the kidney or in the body.

Could we say with certainty of a given diuretic that it is a stimulant of the renal glandular epithelium, we might also predict with certainty of it that it would, on the one hand, increase the diuretic effect of digitalis, and that, on the other hand, its diuretic effect would be increased by digitalis. We would further be enabled to judge when one or other or both drugs might be administered safely and with advantage.

Now, various facts brought out in my clinical experience of citrate of caffein as a diuretic have led me to believe that the diuretic action of this drug is due, *for the most part*, to a power which it possesses of stimulating the renal glandular epithelium.

The evidence brought forward by Drs Gubler, Lewis Shapter, and Leech is amply sufficient to prove that in cases of cardiac dropsy especially, and also in some other forms of dropsy, caffein is a powerful diuretic. It is quite unnecessary that I should occupy space in this paper with the many cases in which I have found the conclusions arrived at by these observers regarding the remarkable diuretic action of this drug fully confirmed. I will rather direct attention to the circumstances which seem to modify the action of the drug, on the one hand diminishing or preventing it, and on the other hand assisting and increasing it. Thus we may hope to arrive at a more accurate understanding of its mode of action, and the reasons of the apparent variability of its effects in different cases, or in the same case at different times; and also to gain some more precise ideas regarding the cases in which it should be employed, and how it may be administered with most advantage in these cases.

What are the actions claimed for citrate of caffein by previous observers, in virtue of which it is believed to produce its diuretic effect? The results obtained and the conclusions arrived at by physiologists, which bear upon the action of caffein as a diuretic, have been most conflicting. It has been claimed by trustworthy observers that under the influence of this drug the blood-pressure and the amounts of urea and carbonic acid eliminated are all increased; and by equally reliable observers that they are all diminished, and so forth. These opposite results are doubtless due to differences in the animals experimented on, and the size of the doses employed.

Binz states that "in moderate doses it increases the heart's action, both by its direct effect on the organ and also by exciting contraction of the arteries. The blood-pressure and the frequency of the pulse are intensified. There is a very rapid rise of temperature, which in animals may exceed 1·5° Cent. More urea and carbonic acid are excreted and urine secreted than in the normal state. All these symptoms are of relatively short duration. One part of the caffein is excreted in the urine soon after its introduction into the system." [1]

Drs Gubler, Shapter, and Leech have all recognised that the above physiological conclusions point to a double action whereby the diuretic effects of citrate of caffein may be explained.

1*st*, It may act as a diuretic in virtue of its power of increasing the action of the heart and the blood-pressure, its action in this respect being like, but not identical with, that of digitalis.

2*d*, It may do so, further, in virtue of a special action which it possesses of directly stimulating the secreting structures in the kidney.

Gubler has pointed out the resemblance of its action in the latter respect to that of jaborandi and other drugs, which by a special action exerted on the secretory nerves of the salivary gland

[1] *Elements of Therapeutics.*

greatly augment the flow of saliva. The resemblance is probably even greater than Gubler supposes, and I purpose in a future paper to show that jaborandi and pilocarpin possess the power of increasing the amount of the urine.[1]

Did citrate of caffein possess markedly both of these properties, it would indeed be a model diuretic, possessing the power to increase the separation of urine both by filtration and secretion. My clinical experience of the drug goes, however, to show that, whatever may be its effect in healthy animals or individuals, in those cases of cardiac and renal dropsy in which its diuretic action is most strikingly manifested this effect must be attributed for the most part, if not entirely, to a remarkable power possessed by the drug of directly increasing the activity of the glandular renal epithelium, and that its action in increasing the general or local blood-pressure, and in this manner the rapidity of the circulation through the kidneys, is, if present at all, its feebler and very much less important action.

The following facts may be adduced as the grounds on which I have been led to this conclusion:—

I. *Disease of the renal glandular epithelium would appear to prevent the action of citrate of caffein altogether.*

In the early stage of acute desquamative nephritis, after all febrile symptoms have subsided, and while such vascular diuretics as digitalis, and other diuretics such as acetate of potash, have proved efficient, citrate of caffein has failed entirely to cause any increase in the amount of urine passed.

Case I.—R. S., aged 44, had been ill for three weeks with acute desquamative nephritis, the result of cold, when he was admitted into Ward 31, New Royal Infirmary, under my care. There was swelling of the eyelids and face, and considerable general anasarca. The urine was scanty, high-coloured, albuminous, and contained granular and hyaline tube-casts. The amounts of urine passed on each of the first three days after admission was 30 oz., 34 oz., and 34 oz. respectively. Citrate of caffein in gr. iij. doses was now administered thrice daily for three days, and the amounts of urine passed on each of these days in their order were 32 oz., 34 oz., and 32 oz. respectively, being a fall rather than an increase under the influence of the drug. The caffein was now stopped, and ten minims of tincture of digitalis with thirty grains of acetate of potash were given instead three times daily. On the following three days 56 oz., 62 oz., and 70 oz. of urine were passed. These results contrast *sharply* and *strongly*.

Case II.—J. U., aged 40, had been ill for ten days with the same disease before his admission into Ward 31. He

[1] See some observations made by me at the Edinburgh Medico-Chirurgical Society on the "Diuretic Action of Jaborandi," *Medical Times and Gazette*, *November* 20, 1875, p. 583.

was very œdematous, there being œdema of the lungs, slight ascites, and general anasarca. In his case the citrate of caffein, given as above, did not give rise to any increase in the amount of the urine. It caused, on the contrary, a slight diminution, as in the last case; and as its administration was followed by sickness, headache, and vomiting, it had to be suspended. Later on in this case the caffein salt was administered with gradually increasing effect; about three weeks after the first trial had failed the urine rose under its administration to 112 ounces.

In both cases perfect recovery resulted. For good reasons I have refrained from multiplying such experiments in the early stage of desquamative nephritis. I have, however, availed myself in many such cases of the hint thus obtained that one or two gr. iij. doses of citrate of caffein might be useful as a test drug to ascertain the condition of the renal epithelium, and many observations thus made have satisfied me of the accuracy of the conclusion which I have drawn from the two cases referred to, in which a more prolonged use of the drug was tried. This absence of any of the usual marked diuretic action of the drug in disease of the renal epithelium points, on the one hand, to the need of the secreting cells for the manifestation of its diuretic action, and, on the other hand, to its independence of any effect on the circulatory organs. The increasing action of the drug as recovery progressed points also in the same direction.

II. *When citrate of caffein acts as a diuretic, not only is the amount of the water in the urine increased, but the amount of urea, when previously abnormally lowered, is markedly increased.*

The quantitative analysis of the urea in the following cases was made for me by Mr John Priestly, of whose scientific ability and accuracy his chapter "On the Contractile Tissues" in Professor Gamgee's work on *The Physiological Chemistry of the Animal Body* is a sufficient guarantee. The diet was not measured in any of the cases, but was maintained at as nearly a uniform standard in each case as possible. The method employed in estimating the urea was Dr Apjohn's modification of the hypobromite of sodium process.

The cases which I give are only three in number, but they are the first three in which the amounts of urea were estimated, and are therefore not selected. The daily amounts of urea passed both before and during the administration of the caffein were measured; and although these cases are few in number, and the interpretation of the results liable to many fallacies, they are important in this respect, that they all show a decided increase in the amounts of urea passed during the administration of the citrate of caffein.

Case I.—W. D., aged 33, suffering from great aortic incompetence, has been under my care since 23d Oct. 1880, suffering from dropsy, breathlessness, and giddiness, etc. During that period the only medicines which have given him any relief have

been digitalis and caffein, which he has taken more or less constantly. It struck me that the citrate of caffein and digitalis gave him much more relief than could be accounted for by the mere increase in the quantity of the water, which was never very high. To satisfy myself I had the amounts of urea and urine measured during four periods.

First, For three days while tincture of digitalis and citrate of caffein were still administered.

Secondly, For three days after the administration of these drugs had been suspended.

Thirdly, For three days during which citrate of caffein was again administered alone.

Fourthly, For several days during which both caffein and digitalis were administered.

During the first period, while both drugs were still given, the daily amounts of urine passed on each of the three days in their order were, 36 oz., 36 oz., and 34 oz. of urine, containing 380·16 grs., 382·69 grs., and 388·96 grs. of urea respectively. The amounts were remarkably steady.

During the second period, when no drugs were given, the daily amounts of urine were, 34 oz., 24 oz., and 22 oz. of urine, containing 359 grs., 264 grs., and 280·72 grs. of urea respectively. We have thus a fall of 12 oz. in the amount of urine, and of over 100 grs. in the amount of urea passed daily.

During the third period gr. iij. of citrate of caffein were administered thrice daily. On the corresponding three days the amounts of urine passed were, 25 oz., 25 oz., and 42 oz., and the amounts of urea contained in each of these, 341 grs., 308 grs., 351·12 grs. Thus we have, without the aid of the digitalis, a rise of 70·4 grs. of urea, or to within 30 grs. of the amount passed while both digitalis and caffein were given together.

During the fourth period, when digitalis was added in ℥x. doses to the citrate of caffein, a very remarkable result followed. The amount of urea rose on the first day from 351·12 grs. to 406·52 grs., and on the second day to 619·52 grs., being an increase in the daily amount in two days of 268·4 grs. I will refer to this last effect of adding digitalis again.

Case II.—P. M'A., aged 45, suffering from mitral stenosis and general anasarca, was admitted into Ward 31, on February 26, 1881. On the first three days after his admission into the Infirmary all medicines which he had previously been taking were suspended, and no other drugs given. The total daily amount of urine passed during this period were, 22 oz., 20 oz., and 38 oz., the corresponding amounts of urea being 222·64 grs., 167·2 grs., and 83·6 grs. Here we had a steady fall in the daily quantity of urea passed, amounting in two days to 139 grs. Citrate of caffein was now given in gr. iij. doses three times daily. A mistake occurred on the first day, whereby the amount of urea was not taken, but on the

second day it amounted to 309·54 grains, a rise in two days in the daily amount of about 206 grains.

I will cite only one other case at present.

Case III.—Thomas C., aged 53, had been ill with chronic desquamative nephritis for four months. The urine was albuminous and contained granular and hyaline casts, and he had albuminuric retinitis. All medicines were stopped, and the amounts of urine passed on the three first days after admission were, 28 oz., 14 oz., and 28 oz. The urea was not estimated on the first day: on the second and third days it amounted to 44·96 grs. and 89·93 grs. respectively. Three grains of citrate of caffein were now given three times daily for three days, and the daily amounts of urine passed on these days were 30 oz., 62 oz., and 54 oz.; the corresponding daily quantities of urea being, 115·8 grs., 272·8 grs., and 314·82 grs., a rise in three days of 224·89 grs. in the daily amount.

The result in each of these cases shows a marked increase in the amount of urea passed under the influence of citrate of caffein.

It is noteworthy that in no case did citrate of caffein alone raise the daily amount of urea above a normal amount, and it should be stated that in all cases the rise under the citrate of caffein was greatest within the first two or three days, falling somewhat afterwards.

From these facts, and from the fact that in all the cases given the amount of urea had *fallen* in quantity when the citrate of caffein was commenced, it would appear that this substance *does not increase the formation of urea in the body, but merely its elimination when it has accumulated so as to be in excess in the blood.* Further evidence in this direction, which is still too incomplete to be adduced here, I hope to give in a future communication.

III. *Further, and perhaps the strongest, arguments in favour of the view that citrate of caffein acts upon the glandular epithelium are to be gathered from a careful study of the separate and combined actions of the two drugs, citrate of caffein and digitalis, in certain cases of cardiac dropsy.*

The following facts—which I have observed in many cases—are especially interesting in this connexion. In cases of extreme cardiac disease with very low arterial blood-pressure and general dropsy, in which the amount of urine passed is very small, if citrate of caffein be administered, in the first instance it will frequently fail to produce any increased diuresis, and will cause sickness, vomiting, and headache. If digitalis be now administered instead of the citrate of caffein, very little effect may apparently be produced by it for some time, the urine remaining about the same in quantity as before. If, however, in these circumstances, citrate of caffein be now administered in addition to the digitalis, a very rapid and great rise in the amount of the urine may result.

I will give one example that well illustrates these facts.

Rebecca H., aged 40 years, was brought into Ward 33 on December 11, 1880, extremely ill. She was found to be suffering from mitral stenosis, with resulting cardiac dilatation, pulmonary œdema, and general anasarca. Her pulse was extremely weak and irregular, and her face and fingers were very cyanotic. There was great œdema of the lungs and ascites.

On the day of her admission two three-grain doses of citrate of caffein were given, *which produced sickness, headache, and vomiting*, but *no rise* in the amount of the urine, which, on the contrary, *fell* from 12 oz. to 10 oz. Ten minims of tincture of digitalis were now given every four hours. On the following day only 8 oz. of urine were passed. The dose was increased to ℥xv., and the next day the amount passed was about the same, but some was lost at stool.

On the following day only 15 oz. were passed. As she was in great distress, it was now determined to add to the digitalis citrate of caffein in gr. iij. doses thrice daily.

The following amounts of urine were passed on the six days after this was commenced:—62, 80, 75, 43, 106, and 139 ounces. It was thus clear that citrate of caffein had added a very powerful influence to that previously exerted by the digitalis. An opportunity was now afforded of studying how much of this action was due to the digitalis, which, when administered alone, had apparently no diuretic action at all.

On the day following that on which 139 oz. had been passed, the digitalis was omitted, and the result was a fall in the amount of the urine to 65 oz. The digitalis was now again resumed, and on the same day the urine rose to 120 oz. Now the behaviour of these drugs, digitalis and citrate of caffein, in this case, is very much like what I have met with in other similar cases. The facts to be explained in this case are the following:—

First, Why, on the first day of treatment, citrate of caffein not only failed to produce any diuretic action, but was positively injurious.

Second, Why digitalis alone in the first instance failed, except to a very slight extent, to increase the urine.

Third, Why, after this, the addition of citrate of caffein to the digitalis suddenly raised the amount of urine in one day from 15 to 62 ounces, and in six days to 139 ounces.

Fourth, Why the intermission of the digitalis for one day caused a sudden fall in the amount of the urine from 139 to 65 ounces, whereas on the re-administration of that drug the urine at once again rose to 120 ounces.

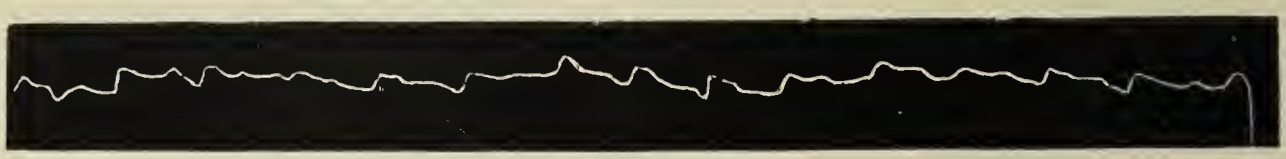
Now I think that these questions can best be answered together.

Two diuretic drugs which thus have both failed to have any decided effect when administered separately, and which have had so remarkable an effect when administered conjointly, must have produced this decided effect either in virtue of some action common to both which has been increased by their combined administration, or because their actions are complementary of one another. The only

action which citrate of caffein and digitalis can be claimed to have in common is an action on the circulatory organs.

Now, if the marked diuresis produced by these drugs in combination were due to an increased action on the circulatory organs, such a diuretic result as 139 ounces of urine in 24 hours should certainly be accompanied with an evident increase in the blood-pressure.

Mr Douie, one of the most careful of my clinical clerks, took for me several sphygmographic tracings in this case on 22d December 1880, when the amount of urine passed was 120 ounces. The pulse on that day was felt to be feeble and very irregular, and the tracings, one of which is given in the figure, presented the same characteristics very distinctly.[1]



Such a condition of the general blood-pressure is quite incompatible with the idea that the exceedingly large amount of urine passed in this case could be the result of filtration from increased blood-pressure.

It therefore must have depended on some other action of the *citrate of caffein*, for digitalis is a purely vascular diuretic.

The only other action which has been claimed for citrate of caffein is an action on the renal glandular epithelium similar to that which urea has been shown to possess, and perhaps like in nature to that of pilocarpin on the salivary glands. All the foregoing evidence points in this direction.

That the actions of these two drugs are complementary of one another is further probable from the fact that while each alone signally failed to produce diuresis, the two together immediately produced a very marked result. Assuming, then, that these drugs are complementary of one another in their diuretic action, and falling back on our conclusions regarding the physiology of diuresis, this view is further supported by the fact that it will be found to explain all the difficulties in this and other similar cases. Thus—

1*st*, Citrate of caffein failed to act at first because, the blood-pressure being very low, a transference of work must have taken place from the filtering to the secreting structures in the kidney, and the renal epithelium, being consequently overworked or exhausted, could not be further stimulated.

2*d*, Digitalis failed to produce any marked diuresis at first, because the slight increase in the blood-pressure and in the amount of blood passing through the kidney led, in the first place, to an

[1] Dr G. A. Gibson has kindly allowed me to refer to some unpublished experiments recently performed by him in Professor Fraser's laboratory, and under Professor Fraser's observation. The series of experiments showed that any increase of blood-pressure as the result of injections of citrate of caffein was either absent or quite insignificant.

increased amount of filtration and a corresponding transference of work back from the secreting to the filtering structures; and, as I have before stated, this is not necessarily represented by an increase in the amount of the urine.

3d, That digitalis, although it had caused no increase in the urine, had in a few days *effected a very decided change* in the *conditions in the kidney*, was now evident; for the same doses of citrate of caffein which at first failed entirely, now, when administered in addition to the digitalis, caused a sudden and extraordinary rise in the urine in one day from 15 to 62 ounces, and in six days to 139 ounces.[1] That the digitalis, which produced no rise in the urine when given alone, contributed to this result was clear from the fact that the omission of it for one day caused a fall in the amount of urine from 139 ounces to 65 ounces, and its resumption a rise again to 120 ounces.

With the low blood-pressure which we had in this case, it is difficult to understand exactly how digitalis modified the conditions in the kidney so as to favour to such a degree the special action of the caffein. We must, however, in the first place, admit that *the secretion of so large an amount of urine is proof in itself that a correspondingly large amount of blood must have circulated through the kidneys.*

It seems to me, however, that only part of this increased circulation can, in a case with such a condition of the pulse as we have here, be fairly attributed to the action of digitalis on the circulation. In addition to this *vis a tergo*, if we admit that citrate of caffein acts as a true secretory stimulant of the renal epithelium, we are compelled further to admit that it must by this action cause an increased *vis a fronte*. For the separation by secretion of a large amount of urine from the blood must proportionally facilitate the passage of the blood through the vessels of the kidney, and consequently increase the amount of blood entering into and passing through that organ.

Further, if this be the case, the amount of urine separated by

[1] It is well known that often, under the digitalis treatment, no marked increase in the amount of the urine may occur until about the third or fourth day, when a very rapid and considerable rise may occur.

This increased diuresis from digitalis is, if very considerable, accompanied by and chiefly due to increased blood-pressure.

The case given is specially selected, because in it the separation of a large amount of urine was associated with a pulse so feeble and irregular as to make it impossible that the diuresis could be due to increased blood-pressure.

Those who maintain—although it has never been demonstrated—that digitalis is a stimulant of the renal secreting structures, admit that this is its lesser and feebler diuretic action, and will hardly maintain that the greatly increased diuresis in this case was due to this action.

Doubtless, in many cases, after transference of work from the secreting to the filtering structures in the kidney has been effected by digitalis, its action as a vascular diuretic becomes rapidly manifested, and the combination of this drug with citrate of caffein is in such circumstances doubly effective.

filtration will be also increased by this *vis a fronte;* for, as we have already seen, the blood-pressure remaining the same, the amount of urine removed from the blood by filtration varies directly with the amount of blood passing through the glomeruli. Thus the vascular and secretory diuretics are in their actions not only complementary of one another, but, further, each promotes the action of the other. In this way we can quite understand the passage of a considerable amount of blood through the kidneys, and the separation of a large amount of urine from it, notwithstanding a low arterial blood-pressure, under the combined actions of digitalis and caffein or other similar combinations, when either alone has failed to have any marked effect.

The further reports of Rebecca H.'s case show that under this plan of treatment the dropsy and other abnormal conditions gradually disappeared. Iron, quinine, and arsenic were after a time substituted for the diuretics. The patient made a good recovery. Her pulse became regular, fairly full and strong, and on 18th January, thirty-seven days after her admission, and about three weeks after the diuretics had been stopped, she passed 78 ounces of water.

We have already seen that citrate of caffein increases the elimination of urea by the kidneys when there has been a previous fall in the amount of urea excreted. It might be expected that if, as I have supposed, digitalis, by increasing filtration and by bringing more blood to the renal epithelium, very markedly increases the action of the caffein, it should manifest this influence by an increase not only in the amount of urinary water excreted, but still more in the amount and percentage of urea. The following cases show this to be the case, and that the increase in the amount of urea is greater than can be accounted for by mere filtration.

In the case of P. M'A., the urea, which under the influence of citrate of caffein alone had risen in two days from 83·6 grs. to 309·54 grs., subsequently fell somewhat, so that on the sixth and seventh days of the administration of that drug it amounted to 277·2 grs. and 280·5 grs. In addition to the citrate of caffein, ten minims of tincture of digitalis were now given three times daily. On the following day the amount of urea was 362·2 grs., being an increase in one day of 84·7 grs.

In the case of W. D. we have already seen that the daily amount of urea, which fell when the administration of citrate of caffein and digitalis was suspended, rose under the administration of citrate of caffein from 280 grs. to 351·12 grs. Digitalis was now added to the citrate of caffein, as in the last case. On the first day the amount of urea rose from 351·12 grs. to 406·52 grs., and on the second day to 619·52 grs., being an increase in this short period of 268·40 grs. per diem. But it is still more interesting to note that while ordinarily, other things being equal, although an increase in the amount of the urine is usually associated with an increase in the total amount of urea passed,

the percentage of urea is diminished, and *vice versa*, in these cases not only was the amount of the urine and of the total urea increased, but the percentage of the urea was either not diminished or was actually increased.

In the first case the amount of urea per ounce was, both before and after the addition of digitalis, about 9·2 grs. per ounce.

In the second case, before the digitalis was commenced, the proportion of urea was 8·36 grs. per ounce, whereas after the digitalis was commenced the amount was 9·68 grs. per ounce on the first day, and, on the second, 14·08 grs. per ounce.

Let me now gather together the foregoing facts which favour the view that citrate of caffein possesses a special power of stimulating the secreting cells in the kidney, and that its action as a vascular diuretic, if present at all, is very feeble.

1*st*, It fails to produce any increase in the amount of the urine in cases in which the renal epithelial cells are diseased,—as, *e.g.*, in the early stages of desquamative nephritis,—even when vascular and saline diuretics produce a considerable increase.

2*d*, It fails to do so in cases of cardiac dropsy in which, from physiological considerations, we may conclude that the glandular epithelial cells are already doing a maximum amount of work, or are exhausted by transference of work to them from the filtering apparatus.

3*d*, When it acts as a diuretic it increases not only the amount of water passed, but also very markedly the amount of urea, if it has previously been abnormally lowered.

4*th*, Its action is strikingly complementary of that of digitalis, so that, in cases in which both given alone have failed, the two administered together, according to the view suggested, have produced very striking diuretic results.

5*th*, This increase in the amount of the urine may be independent of any increase in the general arterial blood-pressure sufficient to account for it on any theory of general or local blood-pressure.

6*th*, The combination of digitalis with citrate of caffein causes a striking rise in the amount and percentage of urea, which cannot be explained on any filtration hypothesis.

How citrate of caffein stimulates the renal glandular epithelial cells is still a matter of conjecture. Probably its action is similar to that of jaborandi or pilocarpin on the salivary and sweat glands. In a future paper I hope to show that the latter substances have a diuretic action like that of caffein. On the other hand, caffein has been observed in exceptional cases to cause both sweating and salivation.

From the foregoing considerations and my whole experience of this drug, the following practical conclusions regarding the employment of citrate of caffein as a diuretic may be deduced :—

1*st*, In cases in which the renal glandular epithelium is diseased, is already doing a maximum amount of work, or is exhausted, this drug is unsuitable and should not be administered.

2*d*, During recovery from acute desquamative nephritis, when renewal of the renal epithelium has reached a certain point, citrate of caffein cautiously administered has appeared to me to have had a decidedly beneficial effect; possibly in such cases it may exert a trophic as well as a secretory stimulant influence.

3*d*, In such cases, as the arterial blood-pressure is tolerably normal, citrate of caffein should be given alone, not in combination with a vascular diuretic.

4*th*, In cases of cardiac disease, with absence of compensation, and resulting diminution in the blood-pressure and flow of blood through the kidney, general dropsy, and transference of work in the kidney from the filtering to the secreting structures, a vascular diuretic, such as digitalis, must be employed in the first place to restore those conditions in the kidney which are essential to the action of citrate of caffein. For this purpose digitalis should be administered for a short period, one to three or four days, before commencing the citrate of caffein.

5*th*, Citrate of caffein, employed in this manner in conjunction with digitalis, which, for obvious reasons, must not be discontinued when the caffein is commenced, is a diuretic of extraordinary power, acts with great rapidity, and is especially valuable in this respect, that it causes a great increase in the elimination of urea (and probably of other solids) as well as of water.

6*th*, It must, however, be remembered that special and powerful stimulation of any gland, especially if it be in a state of malnutrition, may, and usually does, lead sooner or later to exhaustion, and must, therefore, be regarded as at best a temporary expedient and of limited duration.

7*th*, For this reason very large doses of citrate of caffein should be avoided. I have found gr. iii., administered once, twice, or three times daily, according to the circumstances of the case, amply sufficient for all purposes.

8*th*, Whenever the beneficial effects of the drug have been attained, we should at once endeavour to render them permanent by suitable diet, well-selected chalybeate and other tonic remedies, or other remedial measures indicated by the special circumstances of the case.

9*th*, In cases of very great ascites, in which the blood-pressure in and the flow of urine through the kidneys is interfered with by pressure on the kidneys and the renal arteries and veins, and in which the pressure of the urine within the capsules is increased by pressure on the ureters, neither vascular nor secretory diuretics, alone or combined, can act efficiently until the pressure of the ascitic fluid has been got rid of.

10*th*, The citrate of caffein may be administered either in pill or in solution.

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